SUPPLEMENTARY DATA

How Does Empagliflozin Reduce Cardiovascular Mortality? Insights from a Mediation Analysis of the EMPA-REG OUTCOME Trial

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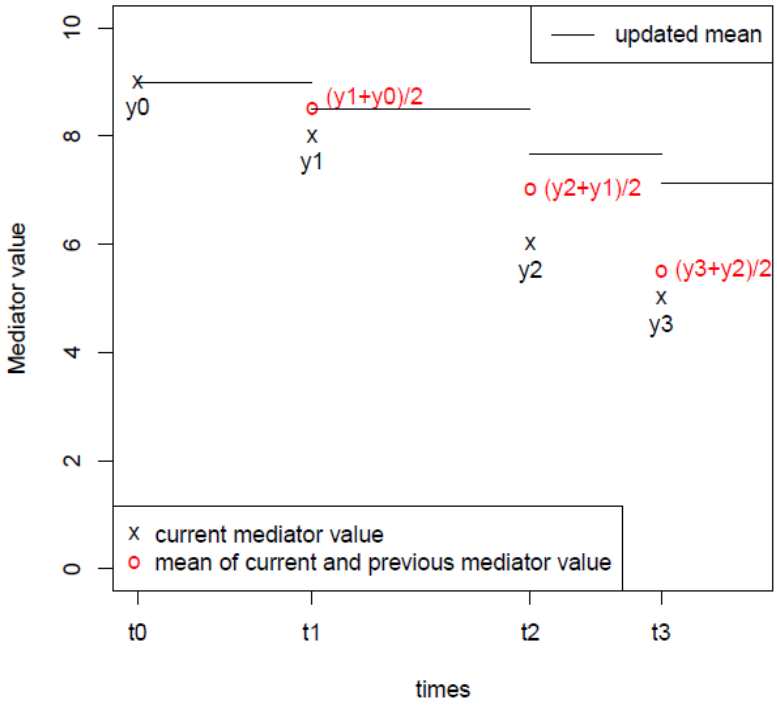
Hypothetical example for illustration of calculation of updated mean of a mediator Y



SUPPLEMENTARY DATA

Supplementary Table S1. Effect of variables on risk of cardiovascular death: time-dependent covariate analysis including the change from baseline in each variable, adjusted for the baseline value of each variable.

	HR for CV death	95% confidence interval
Effect of a 1-unit increase in:		
HbA_{1c} (%)	1.034	0.926, 1.154
FPG (mg/dL)	1.004	1.001, 1.006
SBP (mmHg)	0.989	0.980, 0.997
DBP (mmHg)	0.999	0.984, 1.013
Heart rate (bpm)	1.044	1.033, 1.055
LDL-cholesterol (mg/dL)	1.004	1.000, 1.008
HDL-cholesterol (mg/dL)	0.970	0.953, 0.986
logTriglycerides (1.0 measured on log-scale [log(mg/dL)]	0.627	0.456, 0.864
Free fatty acids (mg/dL)	1.010	0.992, 1.028
logUACR (1.0 measured on log-scale [log(mg/g)])	1.223	1.097, 1.364
eGFR (MDRD) (ml/min/1.73m^2)	0.971	0.962, 0.981
eGFR (CKD-EPI) (ml/min/1.73m^2)	0.968	0.958, 0.977
Weight (kg)	0.967	0.946, 0.990
BMI (kg/m^2)	0.909	0.851, 0.970
Waist circumference (cm)	0.986	0.967, 1.006
Hematocrit (%)	0.901	0.873, 0.930
Hemoglobin (g/dL)	0.705	0.640, 0.776
Albumin (g/dL)	0.156	0.112, 0.219
Uric acid (mg/dL)	1.365	1.255, 1.483

Cox regression analysis in patients treated with ≥1 dose of study drug BMI, body mass index; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease formula; SBP, systolic blood pressure; UACR, urine albumin:creatinine ratio.

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Supplementary Table S2. Effect of variables on risk of cardiovascular death: time-dependent covariate analysis including the updated mean of each variable, adjusted for the baseline value of each variable.

	HR for CV death	**95% confidence interval**
Effect of a 1-unit increase in:		
HbA_{1c} (%)	1.292	1.107, 1.509
FPG (mg/dL)	1.007	1.003, 1.010
SBP (mmHg)	0.997	0.986, 1.009
DBP (mmHg)	1.004	0.984, 1.025
Heart rate (bpm)	1.065	1.047, 1.084
LDL-cholesterol (mg/dL)	1.008	1.003, 1.013
HDL-cholesterol (mg/dL)	0.972	0.950, 0.993
logTriglycerides (1.0 measured on log-scale [log(mg/dL)]	0.824	0.545, 1.245
Free fatty acids (mg/dL)	1.008	0.984, 1.033
logUACR (1.0 measured on log-scale [log(mg/g)])	1.468	1.263, 1.707
eGFR (MDRD) (ml/min/1.73m^2)	0.968	0.955, 0.982
eGFR (CKD-EPI) (ml/min/1.73m^2)	0.964	0.950, 0.978
Weight (kg)	0.971	0.934, 1.010
BMI (kg/m^2)	0.921	0.825, 1.029
Waist circumference (cm)	0.988	0.961, 1.015
Hematocrit (%)	0.890	0.847, 0.934
Hemoglobin (g/dL)	0.690	0.589, 0.809
Albumin (g/dL)	0.068	0.037, 0.125
Uric acid (mg/dL)	1.278	1.122, 1.456

Cox regression analysis in patients treated with ≥1 dose of study drug. BMI, body mass index; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease formula; SBP, systolic blood pressure; UACR, urine albumin:creatinine ratio.

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Supplementary Table S3. Final multivariable analysis built from step-up procedure including variables from different mechanistic categories leading to maximal mediation of treatment effect.
Effects of treatment and variables on risk of cardiovascular death (including the change from baseline in each variable as a time-dependent covariate, adjusted for the baseline value of each variable).

	HR for CV death	**95% confidence interval**	**Percentage mediation**
Effect of empagliflozin vs placebo adjusted for: FPG, logUACR, hematocrit, uric acid	0.931	0.732, 1.183	85.2
Effect of a 1-unit increase in:			
FPG (mg/dL)	1.003	1.001, 1.006	–
logUACR (1.0 measured on log-scale log[mg/g])	1.213	1.089, 1.351	–
Hematocrit (%)	0.919	0.892, 0.947	–
Uric acid (mg/dL)	1.291	1.186, 1.406	–

Cox regression analysis in patients treated with ≥1 dose of study drug. CV, cardiovascular; FPG, fasting plasma glucose; UACR, urine albumin:creatinine ratio.

SUPPLEMENTARY DATA

Supplementary Table S4. Final multivariable analysis built from step-up procedure including variables from different mechanistic categories leading to maximal mediation of treatment effect.
Effects of treatment and variables on risk of cardiovascular death (including the updated mean of each variable as a time-dependent covariate, adjusted for the baseline value of each variable).

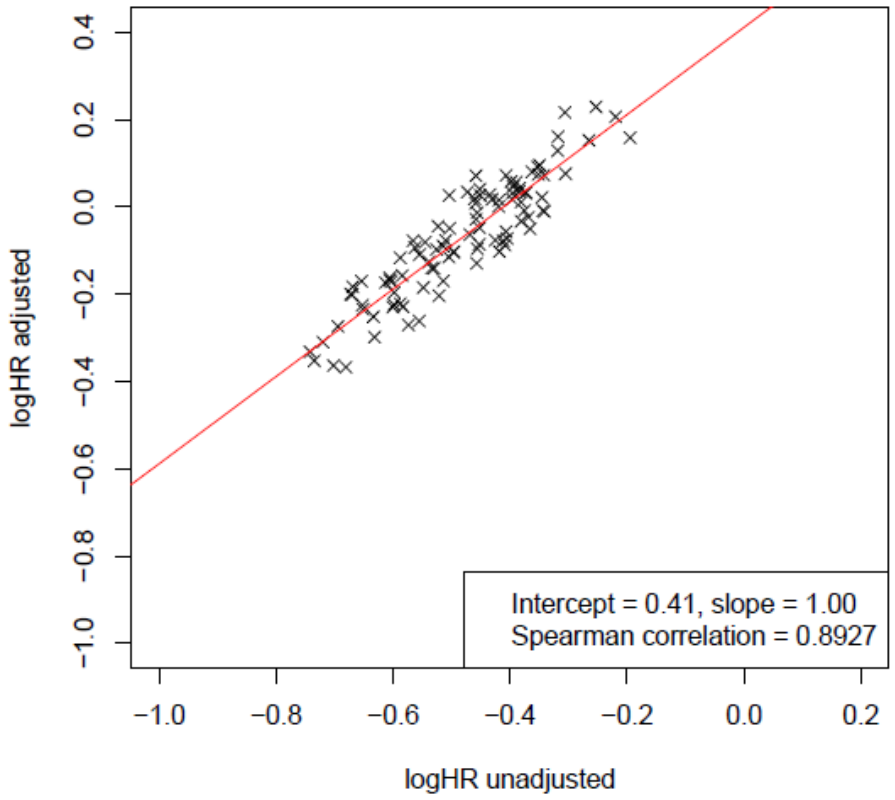
	HR for CV death	**95% confidence interval**	**Percentage mediation**
Effect of empagliflozin vs placebo adjusted for: FPG, logUACR, hematocrit, uric acid	0.974	0.753, 1.261	94.6
Effect of a 1-unit increase in:			
FPG (mg/dL)	1.005	1.002, 1.009	–
logUACR (1.0 measured on log-scale log[mg/g])	1.407	1.209, 1.638	–
Hematocrit (%)	0.909	0.868, 0.953	–
Uric acid (mg/dL)	1.196	1.045, 1.370	–

Cox regression analysis in patients treated with ≥1 dose of study drug. CV, cardiovascular; FPG, fasting plasma glucose; UACR, urine albumin:creatinine ratio.

SUPPLEMENTARY DATA

Supplementary Figure S1. Statistical stability of mediation of treatment effect in multivariable model including the change from baseline of fasting plasma glucose, urine albumin:creatinine ratio, hematocrit, and uric acid as time dependent covariates.

The unadjusted Cox model and the Cox model adjusted for the change from baseline of fasting plasma glucose (FPG), log urine albumin:creatinine ratio (UACR), hematocrit, and uric acid as time-dependent covariates, adjusted for the baseline value of each variable were fit in each of 100 bootstrap samples. In the original data set, the logHR of treatment with empagliflozin vs placebo in the adjusted analysis was –0.07 (difference vs the logHR of the unadjusted analysis: 0.41) and the resulting proportion mediated was 85.2%. The results on mediation of the treatment effect were stable over the bootstrap samples, represented by the intercept of 0.41 estimated from linear regression, corresponding to the estimated difference between unadjusted and adjusted logHR. The median of the proportion mediated estimated in the 100 bootstrap samples was 85.6%.



SUPPLEMENTARY DATA

Supplementary Figure S2. Statistical stability of mediation of treatment effect in multivariable model including the updated mean of fasting plasma glucose, urine albumin:creatinine ratio, hematocrit, and uric acid as time dependent covariates.

The unadjusted Cox model and the Cox model adjusted for the updated mean of fasting plasma glucose (FPG), log urine albumin:creatinine ratio (UACR), hematocrit, and uric acid, as time-dependent covariates, adjusted for the baseline value of each variable were fit in each of 100 bootstrap samples. In the original data set, the logHR of treatment with empagliflozin vs placebo in the adjusted analysis was –0.03 (difference vs the logHR of the unadjusted analysis: 0.46) and the resulting proportion mediated was 94.6%. The results on mediation of the treatment effect were stable over the bootstrap samples, represented by the intercept of 0.47 estimated from linear regression, corresponding to the estimated difference between unadjusted and adjusted logHR. The median of the proportion mediated estimated in the 100 bootstrap samples was 96.5%.